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PATENT & TRADEMARK OFFICE

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Heinz-Josef LENZ et al.
Title:	GENOMIC POLYMORPHISM FOR PREDICTING THERAPEUTIC RESPONSE
Appl. No.:	09/715,764
Filing Date:	November 15, 2000
Examiner:	Sitton, Jehanne Souaya
Art Unit:	1634
Confirmation No.	7045

DECLARATION OF PETER V. DANENBERG UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
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Sir:

I, Peter V. Danenberg, Ph.D, hereby declare as follows:

1. I am Professor of Biochemistry and Molecular Biology at the Keck School of Medicine of the University of Southern California and member of the USC/Norris Cancer Center. I have been studying the correlation between genomic polymorphisms and therapeutic responsiveness of patients to various treatment modalities for over 10 years. My *curriculum vitae* is attached as Exhibit A.

2. I have collaborated with Dr. Heinz-Josef Lenz who is a co- inventor of the above-identified patent application. Dr. Lenz and I are affiliated with the assignee of the above-identified application, namely the University of Southern California.

3. I have read the specification of the above-identified patent application. I have also read the Office Action issued January 27, 2006 by the United States Patent and Trademark Office ("U.S. Patent Office") and the claims currently under examination of this application and the subject of the January 27, 2006 Office Action. I disagree with the opinions of the U.S. Patent Office regarding the teachings of the references cited against the patentability of the pending claims for the reasons set forth below.

4. It is my understanding that the U. S. Patent Office has opined that the invention as set forth in the currently pending claims would have been obvious to one of ordinary skill in the art in view of the teachings of several scientific articles. One of the scientific articles relied upon by the U.S. Patent Office is Horie, et al. *Cell Structure and Function*, 20:191-197 (1995) ("Horie"). I have read the Horie reference and disagree with the Patent Office's characterization of the teachings of this reference.

5. It is my opinion that Horie teaches that a polymorphism exists in the 5' UTR of the thymidylate synthase (TS) gene. Horie notes that this polymorphism may influence mRNA expression levels transcribed from the TS gene. It is my opinion that Horie does not attempt to correlate the existence or absence of the polymorphism with a patient's sensitivity to any therapeutic regime. In fact, Horie states that the polymorphism is found in normal individuals and therefore may not be related to any abnormal physical condition. Horie does not provide any guidance regarding analyzing the polymorphism in the context of sensitivity to a specific therapeutic regime. Additionally, the system employed by and reported in Horie is very different from the system described in the specification of the above-identified patent application. Horie uses an artificial system involving *in vitro* analysis of cells grown in a Petri dish and therefore does not represent cells in their native environment in the body of a patient.

6. The studies reported in Horie determined expression levels of the TS gene using the CAT reporter gene. The specification and pending claims are directed to the levels of mRNA expression isolated from patients and how these levels correlated to the polymorphisms.

7. It is my opinion that one of skill in the art would not interpret the Horie reference as a teaching that polymorphisms in the 5' UTR region of the TS gene could be predictive of therapeutic outcome and/or responsiveness to various therapeutic regimes.

8. I also understand that the U.S. Patent Office cited additional scientific articles that, when combined with Horie, allegedly would lead one of skill in the art to the invention of the currently pending claims. I understand that the article by Leichman, et al., *J. Clin. Oncol.* 15:3223-3229 (1997) is alleged to indicate that TS expression is linked to response to treatment with 5-FU. I disagree because in my opinion, the study reported in this reference only relies on the overall expression level of TS in tumor cells the expression level of which may be unrelated to the 5' UTR polymorphism.

9. The U.S. Patent Office also cited Howells, et al., *Clinical Cancer Res.*, 4:2439-2445 (1998) and Govindarajan, et al., *Proc. Accu. Meet. Am. Soc. Clin. Oncol.*, 17:A2178 (1998), as teaching methods for screening for sensitivity to chemotherapeutic drugs by determining the genotype of a pre-selected gene from normal blood samples and correlating gene expression to sensitivity to the chemotherapeutic drug. However, neither Howells or Govindarajan report on determining the presence of a polymorphism in the 5' UTR region of the TS gene and one of skill in the art could not predict, based on these references, that a polymorphism in the 5' UTR of the TS gene isolated from non-tumor samples would correlate with expression in a pathological cell isolated from an unhealthy individual. Both Howells and Govindarajan involve analysis of the GST family of genes and do not discuss polymorphisms in the TS gene.

10. Therefore, it is my opinion that based on the references cited by the U.S. Patent Office in the January 27, 2006 Office Action, it would not have been obvious to one of ordinary skill in the art to screen for the claimed polymorphism in the 5' UTR region of the TS gene and correlate the results to sensitivity and/or responsiveness to a particular therapeutic regimen.

11. I hereby disclose that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that

these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent that is issued thereon.

July 27, 2002
Dated

Peter V. Danenberg, Ph.D.

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EDUCATION

Case Institute of Technology, Cleveland, OH	B.S. Chemistry 1964
University of Southern California, Los Angeles, CA	M.S. Chemistry 1967
University of California, Santa Barbara, CA	Ph.D. Chemistry 1970

PROFESSIONAL EXPERIENCE

Postdoctoral Fellow, University of Wisconsin, McArdle Laboratory for Cancer Research	1970-1973
Assistant Scientist, University of Wisconsin, Wisconsin Clinical Cancer Center	1973-1976
Assistant Professor, University of Southern California School of Medicine, Department of Biochemistry	1976-1981
Associate Professor, University of Southern California School of Medicine, Department of Biochemistry	1981-1987
Professor, University of Southern California School of Medicine, Department of Biochemistry and Molecular Biology	1987-present

AWARDS AND FELLOWSHIPS

NIH Pre-doctoral Fellowship, 1968-1970.
American Cancer Society Faculty Research Award, 1979-1984.

PROFESSIONAL SOCIETIES

American Association for Cancer Research

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BIBLIOGRAPHY

A. PEER-REVIEWED PAPERS

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B. CHAPTERS, REVIEWS, AND NON-REFEREED PAPERS

1. Danenberg, P.V. and Heidelberger, C., Coupling of 2'-deoxyuridylic acid to sepharose and its use in the purification of thymidylate synthetase. Methods in Enzymology, 34: 521-524, 1974.
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20. Danenberg, P.V. Pharmacogenomics of thymidylate synthase in cancer treatment. Front. Biosci. 9:2484-2494, 2004.

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Danenberg,Kathleen; Danenberg,Peter V.; Swenson; Steven. United States Patent 6,613,518: Quantitative measurement of gene expression based on isolation of RNA from formalin-fixed paraffin-embedded tissue specimens. Issued September 2, 2003.

Danenberg,Kathleen; Danenberg,Peter V.; Swenson; Steven.
United States Patent 6,610,488: Isolation of RNA, DNA and proteins from formalin-fixed paraffin-embedded tissue specimens. Issued August 26, 2003.

Danenberg,Kathleen; Danenberg,Peter V.; Swenson; Steven.
United States Patent 6,428,963: Isolation of RNA from formalin-fixed paraffin-embedded tissue specimens. Issued August 6, 2002.

Danenberg,Kathleen; Danenberg,Peter V.; Swenson; Steven.
United States Patent 6,248,535: Method for isolation of RNA from formalin-fixed paraffin-embedded tissue specimens. Issued June 19, 2001

PROFESSIONAL ACTIVITIES

A. EXTRAMURAL BOARDS

Advisory Panel for Hematologic and Neoplastic Disease Therapy for the U.S.Pharmacopeial Convention, 1980-1986.

Ad hoc reviewer for NIH study sections 18 times since 1981; Ad hoc reviewer for the American Cancer Society; Site visitor for NIH/NCI program project grants 11 times since 1982; Site vistor for CALGB grant, 1997, SPORE grant review committee, 2000, 2001

NCI Developmental Therapeutics Contracts Review Study Section, 1994-1996.

Member, National Cancer Institute Lung Cancer Progress Review Group, 2001.

Consultant for Eli Lilly Co. on development of multi-targeted antifolates, 1994-1999.

Scientific Advisory Board, Response Genetics Co., 2000.

Scientific Advisory Board, Celmed Co., 2004

International Advisory Board for Pharmacogenomics, Eli Lilly Co., 2004

B. EDITORIAL BOARDS:

International Journal of Oncology

Clinical Colorectal Cancer

Clinical Cancer Research

World Journal of Gastroenterology

Current Cancer Therapy Reviews

C. UNIVERSITY COMMITTEES

Medical School Radiation Safety Committee, 1981-83
MD-PhD program development committee, 1991-1993
Alternate representative to the Medical Faculty Assembly, 1979-82
Faculty Senate Representative, 1981-1982
Representative to the Medical Faculty Assembly, 1986
Representative to the Medical Education Curriculum Committee, 1986
Glassware maintenance facility director for the Cancer Research Laboratory 1977-80
Cancer Research Laboratory safety committee, chairman, 1979
Scientific review committee for cancer center pilot grants, 1981, 1982, 1983, 1984, 1985, 1986, 1993, 1994, 1995, 1996, 1997
Cancer Center scientific advisory committee, 1981-1983
Gastrointestinal cancer site team, 1981-1985
Study section for internal career development awards, Children's Hospital of Los Angeles, 1994-1997.
Cancer Center fellowship committee, 1995-1997
Medical School space committee, 1998

TEACHING

Biochemistry 571: Basic Biochemistry
Proteins and enzymes, 8 hours of lecture per year.

Biochemistry 506: Enzyme Kinetics and Mechanisms. Alternate years, 16 hours/semester.

Biochemistry 549: Protein Chemistry and Structure. Conformational changes and protein folding, alternate years, 8 hours/semester.

Biochemistry 501: Cancer Drugs: Biochemistry and Pharmacology. Alternate years, 8 hours/semester.